ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

STARLIX 60 mg film-coated tablets
STARLIX 120 mg film-coated tablets
STARLIX 180 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STARLIX 60 mg film-coated tablets

Each film-coated tablet contains 60 mg nateglinide.

Excipient with known effect
Lactose monohydrate: 141.5 mg per tablet.

STARLIX 120 mg film-coated tablets

Each film-coated tablet contains 120 mg nateglinide.

Excipient with known effect
Lactose monohydrate: 283 mg per tablet.

STARLIX 180 mg film-coated tablets

Each film-coated tablet contains 180 mg nateglinide.

Excipient with known effect
Lactose monohydrate: 214 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

STARLIX 60 mg film-coated tablets

60 mg pink, round, bevelled-edge tablets with “STARLIX” marked on one side and “60” on the other.

STARLIX 120 mg film-coated tablets

120 mg yellow, ovaloid tablets with “STARLIX” marked on one side and “120” on the other.

STARLIX 180 mg film-coated tablets

180 mg red, ovaloid tablets with “STARLIX” marked on one side and “180” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nateglinide is indicated for combination therapy with metformin in type 2 diabetic patients inadequately controlled despite a maximally tolerated dose of metformin alone.

4.2 Posology and method of administration

Posology

Adults
Nateglinide should be taken within 1 to 30 minutes before meals (usually breakfast, lunch and dinner).

The dosage of nateglinide should be determined by the physician according to the patient's requirements.

The recommended starting dose is 60 mg three times daily before meals, particularly in patients who are near goal HbA_{1c}. This may be increased to 120 mg three times daily.

Dose adjustments should be based on periodic glycosylated haemoglobin (HbA_{1c}) measurements. Since the primary therapeutic effect of Starlix is to reduce mealtime glucose (a contributor to HbA_{1c}), the therapeutic response to Starlix may also be monitored with 1–2 hour post-meal glucose.

The recommended maximum daily dose is 180 mg three times daily to be taken before the three main meals.

Special populations

Elderly
The clinical experience in patients over 75 years of age is limited.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment. Although there is a 49% decrease in C_{max} of nateglinide in dialysis patients, the systemic availability and half-life in diabetic subjects with moderate to severe renal insufficiency (creatinine clearance 15–50 ml/min) was comparable between renal subjects requiring haemodialysis and healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. As patients with severe liver disease were not studied, nateglinide is contraindicated in this group.

Paediatric population
There are no data available on the use of nateglinide in patients under 18 years of age, and therefore its use in this age group is not recommended.

Others
In debilitated or malnourished patients the initial and maintenance dosage should be conservative and careful titration is required to avoid hypoglycaemic reactions.

4.3 Contraindications

Starlix is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Type 1 diabetes (C-peptide negative)
- Diabetic ketoacidosis, with or without coma
- Pregnancy and breast-feeding (see section 4.6)
- Severe hepatic impairment

4.4 Special warnings and precautions for use

General

Nateglinide should not be used in monotherapy.

Hypoglycaemia

Like other insulin secretagogues, nateglinide is capable of producing hypoglycaemia.

Hypoglycaemia has been observed in patients with type 2 diabetes on diet and exercise, and in those treated with oral antidiabetic agents (see section 4.8). Elderly, malnourished patients and those with adrenal or pituitary insufficiency or severe renal impairment are more susceptible to the glucose-lowering effect of these treatments. The risk of hypoglycaemia in type 2 diabetic patients may be increased by strenuous physical exercise, or ingestion of alcohol.

Patients with severe renal impairment (see section 5.2) who have not undergone haemodialysis are more susceptible to the glucose-lowering effect of Starlix. Discontinuation should be considered in patients with severe renal impairment who present with potentiation of the hypoglycaemic effect.

Symptoms of hypoglycaemia (unconfirmed by blood glucose levels) were observed in patients whose baseline HbA_{1c} was close to the therapeutic target (HbA_{1c} <7.5%).

Combination with metformin is associated with an increased risk of hypoglycaemia compared to monotherapy.

Hypoglycaemia may be difficult to recognise in subjects receiving beta blockers.

When a patient stabilised on any oral hypoglycaemic agent is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to discontinue oral hypoglycaemic treatment and replace it with insulin on a temporary basis.

Excipients

Starlix contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or of glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

Special populations

Hepatic impairment
Nateglinide should be used with caution in patients with moderate hepatic impairment.

Severe hepatic impairment, children and adolescents
No clinical studies have been conducted in patients with severe hepatic impairment, or in children and adolescents. Treatment is therefore not recommended in these patient groups.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products influence glucose metabolism and possible interactions should therefore be taken into account by the physician.

Combination with ACE-inhibitors, NSAIDs, salicylates, monoamine oxidase inhibitors, non-selective beta-adrenergic-blocking agents and anabolic hormones

The following agents may enhance the hypoglycaemic effect of nateglinide: angiotensin-converting enzyme inhibitors (ACEI), non-steroidal anti-inflammatory agents, salicylates, monoamine oxidase inhibitors, non-selective beta-adrenergic-blocking agents and anabolic hormones (e.g. methandrostenolone).

Diuretics, corticosteroids, beta2 agonists, somatropin, somatostatin analogues, rifampin, phenytoin and St. John's Wort (*Hypericum perforatum*)

The following agents may reduce the hypoglycaemic effect of nateglinide: diuretics, corticosteroids, beta2 agonists, somatropin, somatostatin analogues (e.g. lanreotide, octreotide), rifampin, phenytoin and St. John's Wort (*Hypericum perforatum*).

When these medicinal products - that enhance or reduce the hypoglycaemic effect of nateglinide - are administered to or withdrawn from patients receiving nateglinide, the patient should be observed closely for changes in glycaemic control.

CYP2C9 and CYP3A4 substrates

Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

In an interaction trial with sulfinpyrazone, a CYP2C9 inhibitor, a modest increase in nateglinide AUC (~28%) was observed in healthy volunteers, with no changes in the mean C_{max} and elimination half-life. A more prolonged effect and possibly a risk of hypoglycaemia cannot be excluded in patients when nateglinide is co-administered with CYP2C9 inhibitors.

Particular caution is recommended when nateglinide is co-administered with other more potent inhibitors of CYP2C9 (e.g. fluconazole, gemfibrozil or sulfinpyrazone), or in patients known to be poor metabolisers for CYP2C9 substrates.

Interaction studies with a CYP3A4 inhibitor have not been carried out *in vivo*.

In vivo, nateglinide has no clinically relevant effect on the pharmacokinetics of medicinal products metabolised by CYP2C9 and CYP3A4. The pharmacokinetics of warfarin (a substrate for CYP3A4 and CYP2C9), diclofenac (a substrate for CYP2C9), and digoxin were unaffected by coadministration with nateglinide. Conversely, these medicinal products had no effect on the pharmacokinetics of nateglinide. Thus, no dosage adjustment is required for digoxin, warfarin or other drugs that are CYP2C9 or CYP3A4 substrates upon coadministration with Starlix. Similarly, there was no clinically significant pharmacokinetic interaction of Starlix with other oral antidiabetic agents such as metformin or glibenclamide.

Nateglinide has shown a low potential for protein displacement in *in vitro* studies.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown developmental toxicity (see section 5.3). There is no experience in pregnant women, therefore the safety of Starlix in pregnant women cannot be assessed. Starlix, like other oral antidiabetic agents, must not be used in pregnancy.

Breast-feeding

Nateglinide is excreted in the milk following a peroral dose to lactating rats. Although it is not known whether nateglinide is excreted in human milk, the potential for hypoglycaemia in breast-fed infants may exist and therefore nateglinide should not be used in lactating women.

Fertility

Nateglinide did not impair fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

The effect of Starlix on the ability to drive or operate machinery has not been studied.

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Based on the experience with nateglinide and with other hypoglycaemic agents, the following adverse reactions have been seen. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Hypoglycaemia

As with other antidiabetic agents, symptoms suggestive of hypoglycaemia have been observed after administration of nateglinide. These symptoms included sweating, trembling, dizziness, increased appetite, palpitations, nausea, fatigue, and weakness. These were generally mild in nature and easily handled by intake of carbohydrates when necessary. In completed clinical trials, symptoms of hypoglycaemia were reported in 10.4% with nateglinide monotherapy, 14.5% with nateglinide+metformin combination, 6.9% with metformin alone, 19.8% with glibenclamide alone, and 4.1% with placebo.

Immune system disorders

Rare: Hypersensitivity reactions such as rash, itching and urticaria.

Metabolism and nutrition disorders

Common: Symptoms suggestive of hypoglycaemia.

Gastrointestinal disorders

Common: Abdominal pain, diarrhoea, dyspepsia, nausea.
Uncommon: Vomiting.

Hepatobiliary disorders

Rare: Elevations in liver enzymes.

Other events

Other adverse events observed in clinical studies were of a similar incidence in Starlix-treated and placebo-treated patients.

Post-marketing experience

Post-marketing data revealed very rare cases of erythema multiforme.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In a clinical study in patients, Starlix was administered in increasing doses up to 720 mg a day for 7 days and was well tolerated. There is no experience of an overdose of Starlix in clinical trials. However, an overdose may result in an exaggerated glucose-lowering effect, with the development of hypoglycaemic symptoms. Hypoglycaemic symptoms without loss of consciousness or neurological findings should be treated with oral glucose and adjustments in dosage and/or meal patterns. Severe hypoglycaemic reactions with coma, seizure or other neurological symptoms should be treated with intravenous glucose. As nateglinide is highly protein-bound, dialysis is not an efficient means of removing it from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: D-phenylalanine derivative, ATC code: A10 BX 03

Mechanism of action

Nateglinide is an amino acid (phenylalanine) derivative, which is chemically and pharmacologically distinct from other antidiabetic agents. Nateglinide is a rapid, short-acting oral insulin secretagogue. Its effect is dependent on functioning beta cells in the pancreas islets.

Early insulin secretion is a mechanism for the maintenance of normal glycaemic control. Nateglinide, when taken before a meal, restores early or first phase insulin secretion, which is lost in patients with type 2 diabetes, resulting in a reduction in post-meal glucose and HbA_{1c}.

Nateglinide closes ATP-dependent potassium channels in the beta-cell membrane with characteristics that distinguish it from other sulphonylurea receptor ligands. This depolarises the beta cell and leads to an opening of the calcium channels. The resulting calcium influx enhances insulin secretion. Electrophysiological studies demonstrate that nateglinide has 45–300-fold selectivity for pancreatic beta cell versus cardiovascular K^{+}_{ATP} channels.

Pharmacodynamic effects

In type 2 diabetic patients, the insulinotropic response to a meal occurs within the first 15 minutes following an oral dose of nateglinide. This results in a blood-glucose-lowering effect throughout the meal period. Insulin levels return to baseline within 3 to 4 hours, reducing post-meal hyperinsulinaemia.

Nateglinide-induced insulin secretion by pancreatic beta cells is glucose-sensitive, such that less insulin is secreted as glucose levels fall. Conversely, the coadministration of food or a glucose infusion results in an enhancement of insulin secretion.

In combination with metformin, which mainly affected fasting plasma glucose, the effect of nateglinide on HbA_{1c} was additive compared to either agent alone.

Clinical efficacy and safety

Nateglinide efficacy was inferior to that of metformin in monotherapy (decrease in HbA_{1c} (%) with metformin 500 mg three times daily monotherapy: –1.23 [95% CI: –1.48; –0.99] and with nateglinide 120 mg three times daily monotherapy –0.90 [95% CI: –1.14; –0.66]).

The efficacy of nateglinide in combination with metformin has been compared to the combination of gliclazide plus metformin in a 6-month randomised, double-blind trial in 262 patients using a superiority design. The decrease from baseline in HbA_{1c} was –0.41% in the nateglinide plus metformin group and –0.57% in the gliclazide plus metformin group (difference 0.17%, [95% CI –0.03, 0.36]). Both treatments were well tolerated.

An outcome study has not been conducted with nateglinide, therefore the long-term benefits associated with improved glycaemic control have not been demonstrated.

5.2 Pharmacokinetic properties

Absorption

Nateglinide is rapidly absorbed following oral administration of Starlix tablets prior to a meal, with mean peak drug concentration generally occurring in less than 1 hour. Nateglinide is rapidly and almost completely (≥ 90%) absorbed from an oral solution. Absolute oral bioavailability is estimated to be 72%.

Distribution

The steady-state volume of distribution of nateglinide based on intravenous data is estimated to be approximately 10 litres. *In vitro* studies show that nateglinide is extensively bound (97–99%) to serum proteins, mainly serum albumin and to a lesser extent $alpha_1$-acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1–10 µg Starlix/ml.

Biotransformation

Nateglinide is extensively metabolised. The main metabolites found in humans result from hydroxylation of the isopropyl side-chain, either on the methine carbon, or one of the methyl groups; activity of the main metabolites is about 5–6 and 3 times less potent than nateglinide, respectively. Minor metabolites identified were a diol, an isopropene and acyl glucuronide(s) of nateglinide; only the isopropene minor metabolite possesses activity, which is almost as potent as nateglinide. Data available from both *in vitro* and *in vivo* experiments indicate that nateglinide is predominantly metabolised by CYP2C9 with involvement of CYP3A4 to a smaller extent.

Elimination

Nateglinide and its metabolites are rapidly and completely eliminated. Most of the [14C] nateglinide is excreted in the urine (83%), with an additional 10% eliminated in the faeces. Approximately 75% of the administered [^{14}C] nateglinide is recovered in the urine within six hours post-dose. Approximately 6–16% of the administered dose was excreted in the urine as unchanged drug. Plasma concentrations decline rapidly and the elimination half-life of nateglinide typically averaged 1.5 hours in all studies of Starlix in volunteers and type 2 diabetic patients. Consistent with its short elimination half-life, there is no apparent accumulation of nateglinide upon multiple dosing with up to 240 mg three times daily.

Linearity/non-linearity

In patients with type 2 diabetes who were given Starlix with a dose range of 60 mg to 240 mg before meals three times a day for one week, nateglinide showed linear pharmacokinetics for both AUC and C_{max}. T_{max} was independent of dose.

Special populations

Elderly
Age did not influence the pharmacokinetic properties of nateglinide.

Hepatic impairment
The systemic availability and half-life of nateglinide in non-diabetic subjects with mild to moderate hepatic impairment did not differ to a clinically significant degree from those in healthy subjects.

Renal impairment
The systemic availability and half-life of nateglinide in diabetic patients with mild, moderate (creatinine clearance 31–50 ml/min) and severe (creatinine clearance 15–30 ml/min) renal impairment (not undergoing dialysis) did not differ to a clinically significant degree from those in healthy subjects. There is a 49% decrease in C_{max} of nateglinide in dialysis-dependent diabetic patients. The systemic availability and half-life in dialysis-dependent diabetic patients was comparable with healthy subjects. Although safety was not compromised in this population dose adjustment may be required in view of low C_{max}.

Repeated dosing with 90 mg once daily for 1 to 3 months in diabetic patients with end-stage renal disease (ESRD) showed pronounced M1 metabolite accumulation up to 1.2 ng/ml despite the reduced dose. M1 concentration decreased markedly after haemodialysis. Although M1 metabolites show only slight hypoglycaemic activity (approximately 5 times lower than nateglinide), metabolite accumulation might increase the hypoglycaemic effect of the administered dose. Therefore, dose discontinuation is advisable in patients with severe renal impairment who present with potentiation of hypoglycaemic effect while on Starlix.

Gender
No clinically significant differences in nateglinide pharmacokinetics were observed between men and women.

Pharmacokinetic/pharmacodynamic relationship(s)

Food effect
When given post-prandially, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterised by a decrease in C_{max} and a delay in time to peak plasma concentration (t_{max}). It is recommended that Starlix be administered prior to meals. It is usually taken immediately (1 minute) before a meal but may be taken up to 30 minutes before meals.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to fertility and post-natal development. Nateglinide was not teratogenic in rats. In rabbits, embryonic development was adversely affected and the incidence of gallbladder agenesis or small gallbladder was increased at doses of 300 and 500 mg/kg (approximately 24 and 28 times the human therapeutic exposure with a maximum recommended nateglinide dose of 180 mg, three times daily before meals), but not at 150 mg/kg (approximately 17 times the human therapeutic exposure with a maximum recommended nateglinide dose of 180 mg, three times daily before meals).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

STARLIX 60 mg film-coated tablets

Lactose monohydrate
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Magnesium stearate
Red iron oxide (E172)
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol
Silica, colloidal anhydrous

STARLIX 120 mg film-coated tablets

Lactose monohydrate
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Magnesium stearate
Yellow iron oxide (E172)
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol
Silica, colloidal anhydrous

STARLIX 180 mg film-coated tablets

Lactose monohydrate
Cellulose, microcrystalline
Povidone
Croscarmellose sodium
Magnesium stearate
Red iron oxide (E172)
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Blisters: PVC/PE/PVDC blisters, backed with a heat-sealable lacquered aluminium foil.

Packs contain 12, 24, 30, 60, 84, 120 and 360 tablets.

Not all pack sizes or tablet strengths may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

STARLIX 60 mg film-coated tablets

EU/1/01/174/001-007

STARLIX 120 mg film-coated tablets

EU/1/01/174/008-014

STARLIX 180 mg film-coated tablets

EU/1/01/174/015-021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 April 2001
Date of latest renewal: 24 April 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Farma S.p.A.
Via Provinciale Schito 131
80058 Torre Annunziata (NA)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Starlix 60 mg film-coated tablets
nateglinide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 60 mg nateglinide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

12 film-coated tablets
24 film-coated tablets
30 film-coated tablets
60 film-coated tablets
84 film-coated tablets
120 film-coated tablets
360 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/174/001	12 film-coated tablets
EU/1/01/174/002	24 film-coated tablets
EU/1/01/174/003	30 film-coated tablets
EU/1/01/174/004	60 film-coated tablets
EU/1/01/174/005	84 film-coated tablets
EU/1/01/174/006	120 film-coated tablets
EU/1/01/174/007	360 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Starlix 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Starlix 60 mg tablets
nateglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Starlix 120 mg film-coated tablets
nateglinide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 120 mg nateglinide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

12 film-coated tablets
24 film-coated tablets
30 film-coated tablets
60 film-coated tablets
84 film-coated tablets
120 film-coated tablets
360 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/174/008	12 film-coated tablets
EU/1/01/174/009	24 film-coated tablets
EU/1/01/174/010	30 film-coated tablets
EU/1/01/174/011	60 film-coated tablets
EU/1/01/174/012	84 film-coated tablets
EU/1/01/174/013	120 film-coated tablets
EU/1/01/174/014	360 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Starlix 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Starlix 120 mg tablets
nateglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Starlix 180 mg film-coated tablets
nateglinide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 180 mg nateglinide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

12 film-coated tablets
24 film-coated tablets
30 film-coated tablets
60 film-coated tablets
84 film-coated tablets
120 film-coated tablets
360 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/174/015	12 film-coated tablets
EU/1/01/174/016	24 film-coated tablets
EU/1/01/174/017	30 film-coated tablets
EU/1/01/174/018	60 film-coated tablets
EU/1/01/174/019	84 film-coated tablets
EU/1/01/174/020	120 film-coated tablets
EU/1/01/174/021	360 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Starlix 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Starlix 180 mg tablets
nateglinide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Starlix 60 mg film-coated tablets
Starlix 120 mg film-coated tablets
Starlix 180 mg film-coated tablets
nateglinide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Starlix is and what it is used for

What Starlix is
The active substance of Starlix, nateglinide, belongs to a group of medicines called oral antidiabetics.

Starlix is used to treat adult patients with type 2 diabetes. It helps to control the level of sugar in the blood. Your doctor will prescribe Starlix together with metformin, if inadequately controlled despite a maximally tolerated dose of metformin.

How Starlix works
Insulin is a substance produced in the body by the pancreas. It helps to decrease blood sugar levels, especially after meals. If you have type 2 diabetes, your body may not start producing insulin quickly enough after meals. Starlix works by stimulating the pancreas to produce insulin more quickly, which helps to keep blood sugar levels under control after meals.

Starlix tablets start to act within a very short time after they are swallowed and are eliminated from the body rapidly.

2. What you need to know before you take Starlix

Follow all instructions given to you by your doctor, pharmacist or nurse carefully, even if they are different from what is in this leaflet.

Do not take Starlix
- if you are allergic to nateglinide or any of the other ingredients of this medicine (listed in section 6).
- if you have type 1 diabetes (i.e. your body does not produce any insulin).
- if you are experiencing any symptoms of severe hyperglycaemia (very high blood sugar and/or diabetic ketoacidosis). These symptoms include excessive thirst, frequent urination, weakness, fatigue, nausea, shortness of breath or confusion.
- if you know that you have a severe liver problem.
- if you are pregnant or planning to become pregnant.
- if you are breast-feeding.

If any of these apply to you, do not take Starlix and talk to your doctor.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Starlix.
Diabetic patients may develop symptoms associated with low blood sugar (also called hypoglycaemia). Oral antidiabetics, including Starlix, may also produce symptoms of hypoglycaemia.

If you have low blood sugar you may experience sweating, tremors (feeling shaky), anxiety, difficulty concentrating, confusion, weakness or fainting or have other signs listed in section 4, "Possible side effects".

If this happens to you, eat or drink something containing sugar, and talk to your doctor.

Some people are more likely to get symptoms of low blood sugar than others. Take care:
- if you are over 65 years of age.
- if you are undernourished.
- if you have another medical condition that may cause low blood sugar (e.g. an under-active pituitary or adrenal gland).

If any of these apply to you, monitor your blood sugar levels more carefully.

Watch carefully for signs of low blood sugar, especially:
- if you have exercised more strenuously than usual.
- if you have drunk alcohol.

Talk to your doctor before taking Starlix
- if you know that you have a liver problem.
- if you have a severe kidney problem.
- if you have problems with drug metabolism.
- if you are due to have an operation.
- if you have recently suffered a fever, an accident or an infection.

Your treatment may need to be adjusted.

Children and adolescents
Starlix is not recommended for children and adolescents (under 18 years of age) because its effects in this age group have not been studied.

Elderly
Starlix can be used by people over 65 years of age. Such patients should take special care to avoid low blood sugar.

Other medicines and Starlix
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The amount of Starlix that you need may change if you take other medicines as these may cause your blood sugar levels to go up or down.

It is especially important that you tell your doctor, pharmacist or nurse if you are taking:
- Non-steroidal anti-inflammatory agents (used, for example, to treat muscle and joint pain).
- Salicylates such as aspirin (used as painkillers).
- Monoamine oxidase inhibitors (used to treat depression).
- Beta blockers or ACE inhibitors (angiotensin-converting enzyme inhibitors) (used, for example, to treat high blood pressure and certain heart conditions).
- Diuretics (used to treat high blood pressure).
- Corticosteroids such as prednisone and cortisone (used to treat inflammatory disorders).
- Inhibitors of drug metabolism such as fluconazole (used to treat fungal infection), gemfibrozil (used to treat dyslipidaemia) or sulfinpyrazone (used to treat chronic gout).
- Sympathomimetics (used, for example, to treat asthma).
- Anabolic hormones (e.g. methandrostenolone).
- St. John's Wort, also known as *Hypericum perforatum* (a herbal medicine).
- Somatropin (a growth hormone).
- Somatostatin analogues such as lanreotide and octreotide (used to treat acromegaly).
- Rifampin (used, for example, to treat tuberculosis).
- Phenytoin (used, for example, to treat seizures).

Your doctor may adjust the dose of these medicines.

Starlix with food, drink and alcohol
Take Starlix before meals (see section 3, "How to take Starlix"); its effect may be delayed if it is taken during or after meals.

Alcohol may disturb the control of your blood sugar so you are advised to talk to your doctor about drinking alcohol while taking Starlix.

Pregnancy, breast-feeding and fertility
Do not take Starlix if you are pregnant or planning to become pregnant. See your doctor as soon as possible if you become pregnant during treatment.

Do not breast-feed during treatment with Starlix.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Driving and using machines
Your ability to concentrate or react may be reduced if you have low blood sugar (hypoglycaemia). Bear this in mind if you drive a car or operate machines as you might put yourself or others at risk.

You should ask for doctor advice on driving if you have frequent episodes of hypoglycaemia or if you are not aware of the first signs of hypoglycaemia.

Starlix contains lactose
Starlix tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Starlix contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

3. How to take Starlix

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

The recommended starting dose of Starlix is 60 mg three times daily, taken before each of the three main meals. Your doctor may check the amount of Starlix that you are taking on a regular basis and may adjust the dose according to your needs. The maximum recommended dose is 180 mg three times daily, taken before each of the three main meals.

Take Starlix before meals. Its effect may be delayed if it is taken during or after meals.
Take Starlix before the three main meals, usually:
- 1 dose before breakfast
- 1 dose before lunch
- 1 dose before dinner

It is best to take it right before a main meal but you can take it up to 30 minutes before.

Do not take it if you are not going to eat a main meal. If you miss a meal, skip that dose of Starlix and wait until your next meal.

Swallow the tablets whole with a glass of water.

Even though you are taking medicines for your diabetes, it is important to keep following the diet and/or exercise programme your doctor has recommended for you.

If you take more Starlix than you should
If you have accidentally taken too many tablets, or if someone else takes your tablets, talk to a doctor or pharmacist immediately. Medical attention may be necessary. If you experience symptoms of low blood sugar (listed in section 4, "Possible side effects"), eat or drink something containing sugar.

If you feel as if you are about to have a severe hypoglycaemic attack (which may lead to loss of consciousness or seizure), call for urgent medical help – or make sure that someone else does this for you. If you have to go to a doctor or hospital, take the pack and this leaflet with you.

If you forget to take Starlix
If you forget to take a tablet, simply take the next one before your next meal. Do not take a double dose to make up for a forgotten dose.

If you stop taking Starlix
Continue to take this medicine as long as your doctor prescribes it so that it can continue to control your blood sugar. Do not stop taking Starlix unless your doctor tells you to.

If you have any further questions on the use of this medicine, talk to your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects caused by Starlix are usually mild to moderate.

Common (may affect up to 1 in 10 people):
These are symptoms of low blood sugar (hypoglycaemia), which are usually mild. These include:
- sweating
- dizziness
- shaking
- weakness
- hunger
- feeling your heart beating fast
- tiredness
- feeling sick (nausea)

These symptoms can also be caused by lack of food or too high a dose of any anti-diabetic medicine you are taking. **If you do get symptoms of low blood sugar, eat or drink something containing sugar.**

Other side effects may include:
- Common (may affect up to 1 in 10 people): abdominal pain, indigestion, diarrhoea, nausea
- Uncommon (may affect up to 1 in 100 people): vomiting
- Rare (may affect up to 1 in 1,000 people): mild abnormalities in liver function tests, allergic (hypersensitivity) reactions such as rash and itching
- Very rare (may affect up to 1 in 10,000 people): skin rash with blisters affecting the lips, eyes and/or mouth, sometimes with headache, fever and/or diarrhoea

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Starlix

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
Store in the original package.
Do not store above 30°C.
Do not use any Starlix pack that is damaged or shows signs of tampering.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Starlix contains
- The active substance is nateglinide. Each tablet contains 60, 120 or 180 mg nateglinide.
- The other ingredients are lactose monohydrate; cellulose, microcrystalline; povidone; croscarmellose sodium; magnesium stearate and silica, colloidal anhydrous.
- The tablet coating contains hypromellose; titanium dioxide (E171); talc; macrogol and red (60 and 180 mg tablets) or yellow (120 mg tablets) iron oxide (E172).

What Starlix looks like and contents of the pack
Starlix 60 mg film-coated tablets are pink, round tablets with “STARLIX” marked on one side and “60” on the other.

Starlix 120 mg film-coated tablets are yellow, ovaloid tablets with “STARLIX” marked on one side and “120” on the other.

Starlix 180 mg film-coated tablets are red, ovaloid tablets with “STARLIX” marked on one side and “180” on the other.

Each blister pack contains 12, 24, 30, 60, 84, 120 or 360 tablets. Not all pack sizes or tablet strengths may be available in your country.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu